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(71) Applicants (for all designated States except US):
PALUMED SA [FR/FR]; Prologue Biotech, Rue Pierre et
Marie Curie, F-31319 LABEGE CEDEX (FR). **CENTRE**
NATIONAL DE LA RECHERCHE SCIENTIFIQUE
(CNRS) [FR/FR]; 3, Rue Michel-Ange, F-75794 PARIS
CEDEX (FR).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **BOLDRON**,
Christophe [FR/FR]; "Tout va bien", 30, Place Sylvain

Dumon, F-82400 VALENCE D'AGEN (FR). **PITIE**,
Marguerite [FR/FR]; 17, Rue Romain Rolland, F-31520
RAMONVILLE (FR). **MEUNIER, Bernard** [FR/FR]; 7,
Impasse des Meuniers, F-31320 CASTENET (FR).

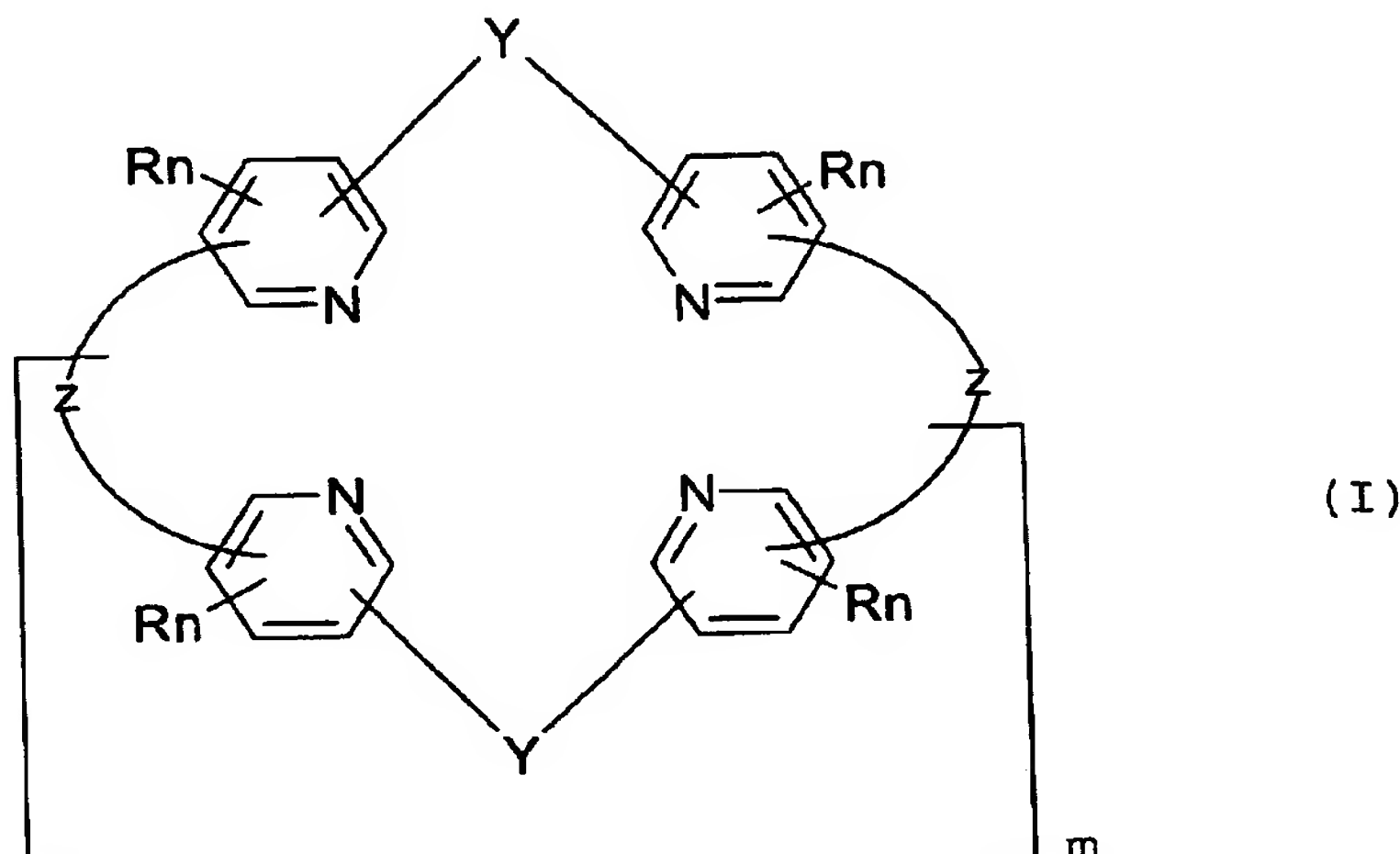
(74) Agents: **PEAUCELLE, Chantal** et al.; Cabinet ARMEN-
GAUD AINE, 3, Avenue Bugeaud, F-75116 PARIS (FR).

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(54) Title: NITROGENEOUS POLYCYCLIC DERIVATIVES USEFUL AS CHELATORS OF METAL IONS AND THEIR AP-
PLICATIONS



(57) Abstract: The invention relates to the use of nitrogeous polycyclic derivatives for preparing drugs for treating neurodegenerative diseases, said derivatives having formula : (I) wherein R_n is R₁, R₂, R₃ and R₄, identical or different and represent H or one or several radicals selected in the group comprising -OH, alkyl, -O-alkyl, -NH₂, -NH-alkyl, -N (R₅, R₆), the alkyl being a C₁-C₆ alkyl, or an halogen, - Y forms a phenyl with both pyridines, optionally ortho-substituted by R₅, or ortho-disubstituted by R₅ and R₆, said substituents, identical or different, being selected amongst alkyl, -O-alkyl, -NH₂, -NH-alkyl, -N (R₅, R₆), the alkyl being a C₁-C₆ alkyl, or an halogen, or represents -(CH₂)_{m1}-W-(CH₂)_{m2}, with M₁ and M₂ being 0, 1 or 2, and W being a group -CH₂-, -CH-(R₇), 0, or N (R₈, R₉), R₇, R₈ and R₉, identical or different, being a C₁-C₃ alkyl radical, or H, - Z is -A-(CH₂)_m-U-(CH₂)_n-A-, with A = O or N, and U = -(CH₂)_n-, -N(R₁, R₂), -COOH, -OH, with n is 2 to 6, and n₁ is 0 or 1, and the complexes thereof with transition metals.



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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| A | MURALI DORAISWAMY P: "NON-CHOLINERGIC STRATEGIES FOR TREATING AND PREVENTING ALZHEIMER'S DISEASE" CNS DRUGS, ADIS INTERNATIONAL, AUCKLAND, NZ, vol. 16, no. 12, 2002, pages 811-824, XP009033332 ISSN: 1172-7047 page 819-820, paragraph entitled "1.9. Chelation Therapy" ----- --/-- | 1-15 |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Borst, M

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| A | CHERNY R A ET AL: "AQUEOUS DISSOLUTION OF ALZHEIMER'S DISEASE ABETA AMYLOID DEPOSITS BY BIOMETAL DEPLETION" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 274, no. 33, 1999, pages 23223-23228, XP000929630 ISSN: 0021-9258 page 23227-23228, paragraph entitled "Discussion" | 1-15 |
| A | CHERNY ROBERT A ET AL: "Treatment with a copper-zinc chelator markedly and rapidly inhibits beta-amyloid accumulation in Alzheimer's disease transgenic mice" NEURON, vol. 30, no. 3, June 2001 (2001-06), pages 665-676, XP002292658 ISSN: 0896-6273 cited in the application page 670-673, paragraph entitled "Discussion" | 1-15 |
| A | WO 98/40071 A (GEN HOSPITAL CORP ; BUSH ASHLEY I (US); ATWOOD CRAIG S (US); HUANG XUD) 17 September 1998 (1998-09-17) claim 8 | 1-15 |
| A | BOLDRON C ET AL: "Simple and efficient syntheses of 1,10-phenanthrolines substituted at C3 or C3 and C8 by methoxy or hydroxy groups" SYNLETT 2001 GERMANY, no. 10, 2001, pages 1629-1631, XP001183054 ISSN: 0936-5214 cited in the application figure and scheme 2 | 1-15 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

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| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
|---|---|---------------------|----------------------------|---------------------|
| WO 9840071 | A | 17-09-1998 | AU 748768 B2 | 13-06-2002 |
| | | | AU 6548498 A | 29-09-1998 |
| | | | CA 2284170 A1 | 17-09-1998 |
| | | | EP 1007048 A1 | 14-06-2000 |
| | | | JP 2001514661 T | 11-09-2001 |
| | | | WO 9840071 A1 | 17-09-1998 |